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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KATCHEVES, KONSTANTINA T	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,457	MANOSROI ET AL.	
	Examiner	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-53* is/are pending in the application.

4a) Of the above claim(s) *23,25,45 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-22,24,26-44 and 48-53* is/are rejected.

7)☒ Claim(s) *46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/9/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

New claims 12-53 are pending in the present application. Original claims 1-11 were cancelled in the amendment filed 16 December 2003. This Office action is in response to Applicant's amendment and remarks filed 16 December 2003.

Election/Restrictions

Newly submitted claims 23, 25, 45 and 47 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claims 1-53 are comprised of multiple inventions which are methods drawn to different and distinct sequences of tissue plasminogen activators as set forth in claims 23, 25, 45 and 47 which do not render obvious each other and thus are patentably distinct. The methods of producing recombinant heterologous protein, e.g. tissue plasminogen activator, represent unrelated, independent and patentably distinct inventions when drawn to expressing separated and distinct sequences in the newly filed claims 23, 25, 45 and 47. The sequences newly claims are amino acids 50-87 of SEQ ID NO:18, amino acids 4-50 of SEQ ID NO:18, amino acids 86-176 of SEQ ID NO:18, amino acids 176-262 of SEQ ID NO:18, amino acids 276-527 of SEQ ID NO:18, SEQ ID NO:10, SEQ ID N0:11, SEQ ID N0:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO: 16, and SEQ ID NO : 17.

As mentioned above, because each of the above-cited sequences are separate and distinct from each other, a method for expressing each of these sequences is a separate and distinct invention because the sequences themselves are patentably distinct from each other. Inventions of Groups III-VII are biologically and functionally different and distinct from each other and

thus one does not render the other obvious. The methods of expressing each of these proteins comprise steps which are not required for or present in the methods of expressing each of the others: a construct comprising amino acids 50-87 of SEQ ID NO:18, a construct comprising amino acids 4-50 of SEQ ID NO:18, a construct comprising amino acids 86-176 of SEQ ID NO:18, a construct comprising amino acids 176-262 of SEQ ID NO:18, a construct comprising amino acids 276-527 of SEQ ID NO:18, a construct comprising SEQ ID NO:10, a construct comprising SEQ ID NO:11, a construct comprising SEQ ID NO:12, a construct comprising SEQ ID NO:13, a construct comprising SEQ ID NO:14, a construct comprising SEQ ID NO:15, a construct comprising SEQ ID NO: 16, and a construct comprising SEQ ID NO:17.

The end result of the methods are also different: producing a finger domain, producing a growth factor domain, producing Kringle domain 1, producing Kringle domain 2, producing a Protease domain, and producing eight different mutants of the K2S variant of tissue plasminogen activator (tPA). Thus, the operation, function and effects of these different methods are different and distinct from each other. Moreover, the end results of each of these methods differ. Therefore, the inventions of these different, distinct groups are capable of supporting separate patents.

Moreover, the search of these sequences would represent an undue search burden to the examiner for a number of reasons. First, the genus of tissue plasminogen activators has been previously examined. A search of this broad category of protein is not necessarily coextensive in scope with the specifically claimed polypeptides in claims 23, 25, 45 and 47. Second, Applicant should note at the outset that the search multiple sequences presents a serious search burden for the examiner particularly considering that the size of Genbank, alone, far exceeded five million

entries in 1997 and has been growing exponentially since and because each claimed sequence must individually be compared to each entry in each of the databases available to the Examiner.

Applicant should also note that SEQ ID NO:2 and SEQ ID NO:4, which were not previously examined, have also been added with the newly filed claims. As a courtesy to Applicant, SEQ ID NO:2 and SEQ ID NO:4 will be examined although they are separate and distinct from the polypeptide encoded by SEQ ID NO:5 that has been examined in the originally filed claims.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 23, 25, 45 and 47 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Accordingly, Claims 12-22, 24, 26-44, 46 and 48-53 are currently under examination.

Response to Amendment

In view of the cancellation of claims 1-11 and the presentation of new claims 12-53 in the amendment filed 16 December 2003, the rejections of claims 1-11 set forth in the Office action mailed 16 July 2003 have been rendered moot. However, Applicant's arguments will be addressed insofar as those rejections are applicable to the newly presented claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31-33, 39, 52 and 53 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 and 10 of copending Application No. 09/987455 (US 2003/0049729). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 31-33, 39, 52 and 53 are generic to all that is recited in claims 1-6 and 8-10 of copending Application No. 09/987455. That is, claims 1-6 and 8-10 of copending Application No. 09/987455 fall entirely within the scope of claims 31-33, 39, 52 and 53, or in other words, claims 31-33, 39, 52 and 53 are anticipated by claims 1-6 and 8-10 of copending Application No. 09/987455. Specifically, the1 present claims are drawn to a method of producing a recombinant protein which is a tissue plasminogen activator which is operably linked to the OmpA signal peptide wherein the protein

is secreted properly folded and expressed in *E.coli*. A lac promoter and/or ribosomal binding site precede the DNA encoding the heterologous protein. The claims of copending Application No: 09/987455 recite these same limitations. The copending claims are drawn to a method of producing a recombinant tissue plasminogen activator that is secreted extracellularly as a correctly folded protein wherein the protein is operable linked to an OmpA sequence, the cell used is an *E. coli* cell and the DNA encoding the tissue plasminogen activator is preceeded by a lac promoter and/or a ribosomal binding site.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31-33, 39, 52 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Georgiou et al. (US Patent No. 6,027,888; Applicant's IDS).

The invention of the instant claims are drawn to a method of producing a recombinant tissue plasminogen activator in prokaryotic cells comprising expressing a vector which comprises DNA encoding tissue plasminogen activator operably linked to DNA encoding the OmpA signal peptide wherein said tissue plasminogen activator (human) is secreted extracellularly as an active, correctly folded protein.

Georgiou et al. teach a method of producing a correctly folded human tissue plasminogen activator in E.coli cells by expressing a construct encoding said activator operably linked to OmpA. See column 4, line 36; column 5, line 50-column 6, line 7; claim 9 and claim 37. The prokaryotic hosts used in the present method include *E.coli* cells. See column 6, line 6.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-22, 24, 26-44 and 48-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is established by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc.,

that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Applicant's claims are drawn to a method of expressing any heterologous protein, a tissue plasminogen activator or a fragment thereof. These claims are drawn broad genuses of polypeptide for which no structure-function relationship has been described. In other words this peptide, sequences and human tissue plasminogen activator have undefined modification while still retaining their respective activity or function. As such, these genus claims encompass a wide array of molecules. The specification does not disclose any of the claimed fragments or variants of tissue plasminogen activator that are embraced by the breadth of these claims. Moreover, the specification fails to provide any teachings as to how the structures of these sequences relate to their function. Thus, the specification does not describe the complete structure of a representative number of species of the claimed genuses. Absent teachings and guidance as to the structure-function relationship of these molecules, the specification does not describe the claimed molecules in such full, clear, concise and exact terms so as to indicate that Applicant had possession of these molecules at the time of filing of the present application.

Applicant's arguments presented in the paper filed 16 December 2003 assert that the specification discloses: "domains or subunits or variants of tPA" which include "the finger domain, the growth factor domain, the Kringle 1 domain, the Kringle 2 domain, the protease domain, and the Kringle 2 plus serine protease (K2S) domain. See Specification, page 14, paragraphs (0058) and (0059)." See Applicant's remarks, page 12. Applicant's arguments are noted. However, the disclosure of the specification fails to adequately disclose these domains. Applicant's specification discloses:

> [tPA] proteins according to the invention may include one, several or all of the following *domains or subunits or variants thereof*:
>
> 1. Finger domain (4-50)
> 2. Growth factor domain (50-87)
> 3. Kringle 1 domain (87-176)
> 4. Kringle 2 domain (176-262)
> 5. Protease domain (276-527)[emphasis added]. See Specification, page 14, paragraph [0058].

The specification, which Applicant relies upon for support, discloses that the tPA protein may include the functional domains disclosed, however, they also may include "subunits or variants thereof." Therefore, the question is whether Applicant has possession of the active tPA of the claims where the functional domains of tPA also include any number of fragments of variants without further disclosure of how much of each of those domains is enough to produce an active protein.

Allowable Subject Matter

Claim 46 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (571) 272-0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Konstantina Katcheves

JAMES KETTER
PRIMARY EXAMINER